ERYTHEMA INFECTIOSUM - A MILD ILLNESS OF MOTHER CAN BE FATAL FOR FOETUS

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Abstract

Erythema infectiosum is one of the expressions of parvovirus B19 a mild self-limiting illness with flu like symptoms followed by a typical facial rash. Although it is more common in children, it can affect at any age but half of the women in reproductive period are immune to the infection and half are susceptible. Infection during pregnancy can lead to foetal infection and may present as non-immune hydrops fetalis a condition which stems from anaemia where there is accumulation of fluid or oedema in at least two compartments of the foetus and severe form of which can lead to foetal death. Destruction of erythroid precursors plays a central role in its pathogenesis. Routine screening of the antenatal blood sample would enable the pregnant women to determine the risk of infection. Risk to the foetus can be reduced with correct diagnosis of the anaemia, USG (Ultrasonography) and treatment by blood transfusion.

Keywords: Erythema infectiosum, Parvovirus, P Antigen

Introduction

Erythema infectiosum or Fifth disease is the commonest manifestation of infections by erthrovirus† or parvovirus B19. It is a small DNA virus icosahedral, non-enveloped, single stranded and measures 23-26 nm in diameter belonging to family Paroviridae, subfamily Parovirinae and genus Erythroparvovirus. It has the capability to invade red blood cell precursors in the bone marrow and in human species it is known to cause disease in paediatric population. It can effect adults also and cause a variety of disorders ranging from erythema infectiosum, papular purpuric ‘gloves and socks’ syndrome‡ and arthropathy in immunocompetent hosts, which is an immune complex, self-limited disorder. Arthritis is non-destructive symmetrical peripheral polyarthritis involving wrists, hands and knees§ which usually resolves within 3 weeks of onset, but small percentage (10-15%) have arthritis which persists for months or even for years¶ to transient aplastic crisis in haemolytic diseases and chronic anaemia in immunocompetent hosts. The patients with haemolytic anaemia like sickle cell anaemia and hereditary spherocytosis who require more production of erythrocytes do not tolerate erythrocyte destructions as do immuno-competent hosts and develop severe aplastic crisis. The patients with immune deficiency may be unable to eliminate B19 infection because of their inability to produce adequate levels of virus specific immunoglobulin G (IgG) antibodies which results in persistent infection with destruction of erythroid precursor cells in the bone marrow and chronic transfusion dependent anaemia to foetal infection manifested by miscarriages, hydrops fetalis and intra uterine device (IUD).** Less than 10% of maternal infections by parvovirus, lead to foetal death when infection is severe and occurs in early gestation before 20 weeks. The death is attributed to development of non-immune hydrops fetalis where in foetus succumbs to severe anaemia and congestive heart failure as foetus requires higher red cell production than adults do and has an immature immune system. It is of importance to obstetricians because of the association with perinatal morbidity and mortality. Fifty percent of women in child bearing age are seropositive and immune to infection§ and fifty percent are susceptible, especially those who work at day care centres or primary schools. Infection is spread by respiratory droplets and transfusion of blood or blood products. The outbreak occurs in winter or spring months with secondary attack rate of 50% for house hold contacts and half of that for classroom contacts.†† Symptoms begin six days after exposure and lasts for a week. Infected patients with normal immune system are contagious before becoming symptomatic but not after that.‡‡ Women who lack P antigen also known as globoside are congenitally immune to parvovirus B19 infection§§ as P antigen is the cellular receptor for parvovirus B19. Serological testing is recommended in pregnant women with nonspecific flu like symptoms with rashes or joint pains and those with foetal hydrops with no other obvious cause. Their serum should be monitored for IgM antibodies to the virus, elevated levels of alpha-fetoprotein, Human Chorionic Gonadotropin (HCG) and Ultrasonography (USG) of foetus for hydrops.

Clinical presentation

Twenty five percent of pregnant women with parvovirus B19 infection are asymptomatic. Others may present with:

- Erythema infectiosum or fifth disease also called apple sickness or ‘ringobayou’ in Japan and ‘butterfly pose’ in Hungary. The commonest manifestation of parvovirus
infection is an immune illness with a typical facial rash which is bright red rash of cheeks with relative pallor around the mouth sparing the naso labial folds, forehead and mouth giving it a slapped cheek appearance. This rash is preceded by low grade fever, mild headache, myalgia and followed by 'lance like' or reticular rash on trunk or extremities with multiple joint pains which is a painful inflammatory symmetrical peripheral polyarthritis and is non-destructive. Teratogenicity of parvovirus infection has not been clearly established and risks of foetal infection depends on gestational age at which infection occurs.

- Maternal infection rate is high when infection occurs in trimester and is 19% & 15% when infection occurs between 13-20 weeks as foetal immune system is immature with in ability to produce significant IgM. Maternal antibodies cross the placenta more readily in the third trimester and during the third trimester, red cells contain more adult type haemoglobin thus red cell life span is longer and foetuses may present with miscarriage, non-immune hydrops, myocarditis and congestive heart failure, IUD (Intra uterine death) and still birth when infection is severe.
- Rarely neonates born to parvovirus B19 infected mothers present with hepatic disease, transfusion related anaemia, myocardial and CNS abnormalities like arthrogyroposes, ventriculomegaly, periventricular calcification and cerebral atrophy.

Morbidity and mortality

The observed rate of foetal death throughout pregnancy is 6.3% and for those infected in the first 20 weeks of gestation is 9-11% that is 1 in 10 women infected with parvovirus B19 will suffer a foetal loss. The observed still birth rate is 0.6% and the overall risk of hydrops fetalis is 3-4%.

Pathogenesis

Infection with parvovirus B19 has two phases; first phase is characterised by viremia that develops six days after intranasal inoculation of PB19 into susceptible individuals who lack serum antibodies to the virus. This phase lasts for about one week, its clearance is correlated with the development of IgM antibodies to parvovirus B19, which remain detectable for up to few months. IgG antibodies develop several days later and persist throughout life. The virus has prediction for the haemopoietic system by binding to a specific cellular receptor erythrocyte P antigen thus destroying the erythroid progenitor cells particularly pronormoblasts and normoblasts and can also infect the endothelial cells and the myocardium. Clinically significant drop in haemoglobin concentration is noted and is maintained for 7 to 10 days with marked depletion of erythroid precursors. Neutropenia, lymphopenia, and mild drop in platelet count may be noted. Second phase begins around 17-18 days after virus inoculation.

Diagnosis

Diagnosis depends on testing maternal serum for parvovirus B19 specific IgM and IgG antibodies which can be detected by commercially available immunoassay kits. Maternal serum IgM appears by third day of symptoms and typically disappears by 30 to 60 days but may persist up to 120 days. IgG antibodies appear by day 7 of illness and persists for life. Immuno-compromised women may not mount an antibody response to the virus and polymerase chain reaction (PCR) testing may be necessary to confirm maternal infection. Diagnosis of foetal infection is by USG examination for the development of hydrops. Serial weekly USG for 8-10 weeks after acute illness of mother should be done to detect foetal anomalies. PCR on foetal blood can be done to detect parvovirus antigens. Cordocentesis or amniocentesis for PCR testing of parvovirus DNA is not recommended.

Treatment

Till now there is no treatment that directly targets the parvovirus B19. Treatment is supportive as the infection is self-limiting. Antipyretics may be used. Prophylaxis of B19 infection with immunoglobulin can be given for susceptible pregnant women. Intaunterine transfusion in foetuses with hydrops foetalis with low reticulocyte count can prevent foetal death. Single transfusion with packed red cells raise foetal haematocrit to 45% and may be sufficient as foetal red cell aplasia is transient and related to period of viremia.

Prevention

Previously, treatment of persistent parvovirus B19 infection was intravenous immunoglobulins which provided resolution of abnormal blood counts. However, because of complications including myocardial infarction, thrombotic events and acute renal failure (osmotic nephrosis), passive immunity with immunoglobulins has not been used. Osmotic nephrosis/cellular swelling and occlusion of the tubular glubulins lumen is one of the most serious and potentially lethal toxicities of immunoglobulins. Recently, several studies including a randomized, double blind phase 1 trial' has reported a recombinant human parvovirus B19 vaccine composed of the VP1 and VP2 capsid proteins and formulated with MF59C.1. All volunteers became parvovirus B19 seropositive after receiving at least 2 doses of the vaccine. There were no deaths or serious adverse events during the study. In September 2007, in US the National Institute of Allergy and Infectious Diseases initiated a phase 1, phase 2 study of the safety and immunogenicity of a recombinant human parvovirus B19 vaccine.

The vaccine could be used to prevent transient aplastic crisis in patients with sickle cell disease or other haemolytic anaemia and in immunodeficient patients with pure red cell anaemia and to prevent persistent arthropathy in adults or in parvovirus B19 seronegative women with hydrops foetalis when inoculated during early pregnancy.
Conclusion

Erythema infectosum an infection by parvovirus B19, a mild illness of pregnant women is an important cause of non-immune hydrops foetalis and represents a risk to the unborn child with marked foetal anaemia and hydrops fetalis or even foetal death. Early diagnosis of foetal anaemia by serial USG allows treatment with intrauterine blood transfusions and is usually successful.

References